REMARKS

Status of Claims and Amendment

This Amendment, filed in reply to the Office Action dated January 12, 2009, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claim 1 has been amended. Claims 2 and 3 have been previously canceled. Claims 1 and 4-6 are all the claims pending in this application, and are rejected.

Claim 1 is amended to further clarify that the liposome is prepared by combining the recited membrane components (i), (ii), and (iii) in a mixture at the same time. Support for the amendment to Claim 1 can be found, for example, at Example 2 (page 8) of the present specification.

No new matter is added.

Response to Rejection of Claims 1 and 4-6 Under 35 U.S.C. § 103

1. Claims 1 and 4-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over EP 0583 665 ("EP '665"), in combination with Aikawa (7,101,532; "Aikawa I") or Kitaguchi (7,008,614; "Kitaguchi") or Schmidt (6,077,529; "Schmidt"), or Mjalli (7,087,632; "Mjalli"), individually or in combination.[1]

The Office Action asserts that EP '665 teaches liposomes containing phosphatidylcholine (PC) and phosphatidylserine (PS) in a 1:1 molar ratio. The Office Action appears to admit that

[1] Applicants note that there are two paragraphs numbered "2" at page 2 of the Office Action, in which the rejection is stated slightly differently. Mjalli is cited in the first paragraph numbered "2" and not in the second. Based upon the text of the rejection, it appears the Examiner is relying on Mjalli and Applicants have responded accordingly.

the benzimidazole is separately added to the liposome mixture by stating that the "benzimidazole however, is then added to the medium containing the liposomes." (See page 2, 6th full paragraph of the Office Action). EP '665 is asserted to teach benzimidazole derivatives for the treatment of hyperlipidemia and arteriosclerosis.

Aikawa I, Kitaguchi, and Schmidt are each asserted for the same reasons of record. For brevity, these reasons are not reiterated herein.

Mjalli is asserted for disclosing liposomal formulations containing benzimidazoles for the treatment of arteriosclerosis. The Office Action admits that Mjalli does not specifically teach liposomes containing both PC and PS. Mjalli is stated to "just [teach] that liposomes can be made from a variety of phospholipids" (see col. 37, lines 44-50 of Mjalli).

The Office Action appears to assert that even if the benzimidazole derivatives of EP '665 are not associated with the liposomal membrane, it would have been obvious to one of ordinary skill in the art to encapsulate or associate the benzimidazole derivatives of EP '665 in liposomes since Kitaguchi and Aikawa I each teach that the liposomes are selectively taken up by vascular smooth muscle cells and macrophages and Schmidt teaches that liposomes may be used in handling atherosclerosis. Thus, the Office Action concludes that one of ordinary skill in the art would be motivated to use liposomes as delivery vehicles with a reasonable expectation of success since Mjalli teaches the use of benzimidazole derivatives for atherosclerosis and this, per the Office Action, is suggestive of the use of liposomes as delivery vehicles.

Applicants note that the presently claimed liposome in which the membrane components of (i), (ii), and (iii) are added at the same time, provides a crucial distinguishing feature over the cited art because this feature allows for the incorporation of benzimidazole into the membrane of the claimed liposome. This is consistent with M.P.E.P. § 2113, in which the "structure implied

by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. Furthermore, this feature is responsible for the unexpectedly enhanced uptake of benzimidazole compounds by macrophages as evidenced by the data shown in the Rule 132 Declaration submitted January 17, 2008, which would not have been predictible based upon the disclosures of the cited art.

Thus, for at least the following reasons and those previously argued, the presently claimed invention is neither taught nor suggested by EP '665, Aikawa I, Kitaguchi, Schmidt, or Mjalli, either alone or in combination.

Applicants note the Office Action has failed to establish a *prima facie* case of obviousness because the prior art references do not teach or suggest all the claim limitations. M.P.E.P. § 2143.

First, EP '665 discloses the separate addition of benzimidazole compound to an already formed liposome mixture (see page 33 of EP '665). EP '665 does not teach or suggest incorporation of a benzimidazole compound into liposomes to prepare the presently claimed liposomes wherein the benzimidazole is combined with the lipid components in a mixture at the same time.

Second, Aikawa I and Kitaguchi do not cure this deficiency because Aikawa I and Kitaguchi are each relied upon for merely disclosing a process of adding a compound as an active ingredient after liposomes have formed. Schmidt is even less relevant because Schmidt is merely relied upon for disclosing liposomes to handle arteriosclerosis and extract cholesterol. The addition of Mjalli does not cure the deficiencies of the above references because Mjalli is

merely relied upon for teaching benzimidazole. Thus, none of the cited references teach or suggest the presently claimed liposome wherein the benzimidazole and lipid components are combined at the same time.

Further, one of ordinary skill in the art would not have predicted that benzimidazole could be incorporated in a liposome with a PC:PS ratio of 1:1 based upon the methods disclosed in the cited references. This is demonstrated by Applicants' additional experiments in the Amendment filed June 27, 2007[2], in which the benzimidazole compound is not incorporated into a liposome wherein phosphatidylcholine and phosphatidylserine are in a ratio of 1:1, by using the method disclosed in the cited references, *i.e.*, the benzimidazole compound was added after formation of the liposome. However, when the benzimidazole was added at the time of formation as presently claimed, the benzimidazole was incorporated into the claimed liposome, which would have been unpredictable based upon the disclosures of the cited references.

Moreover, as evidenced by the experimental data in the Rule 132 Declaration submitted January 17, 2008, the presently claimed liposome provides unexpectedly superior incorporation of the claimed benzimidazole compound. The experimental results submitted in the Declaration of January 17, 2008, show that the amounts of the benzimidazole incorporated into the macrophages are the same between the example in which only the benzimidazole was added and

[2] Applicants note that the results successfully demonstrate that the liposome of "PC: PS=1:1" did not incorporate the ^{14}C-labeled 2-methylbenzimidazole, whereas the liposome of the WO 97/35560 composition did incorporate the ^{14}C-labeled 2-methylbenzimidazole. Applicants note that reference to the liposome 1 and liposome 2 (shown on the graph) was inadvertently reversed in the explanation provided at page 10, first full paragraph of the Amendment filed June 27, 2007. That is, liposome 1 is the liposome disclosed in WO 97/35560 and liposome 2 is the claimed liposome (PC:PS=1:1). Thus, the liposome of the present invention cannot be prepared by using the method disclosed in the cited references.

the example in which a liposome of PC and PS in a ratio of 1:1 was added after the addition of the benzimidazole. These results indicate that the simultaneous addition of benzimidazole with PC and PS is crucial. Further, the experimental results in the Declaration show that when the benzimidazole is added together with PC and PS (1:1) upon formation of the liposome, the amount of the benzimidazole incorporated into the macrophages was unpredictably greater than those of Sample 1 and Sample 2.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

2. Claims 1 and 4-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Aikawa (5,387,600; "Aikawa II") of record in view of Aikawa I or Kitaguchi or Schmidt or Mjalli, individually or in combination.

Aikawa II is asserted to teach benzimidazole derivatives for the treatment of atherosclerosis. The Office Action admits that Aikawa II does not teach the use of liposomes as carriers.

Aikawa I, Kitaguchi, Schmidt, and Mjalli appear to be asserted for the same reasons as discussed above.

Thus, the Office Action concludes that it would have been obvious to one of ordinary skill in the art to encapsulate or associate the benzimidazole derivatives of Aikawa II in liposomes since Kitaguchi and Aikawa I each teach that the liposomes are selectively taken up by vascular smooth muscle cells and macrophages, Schmidt teaches that liposomes may be used in handling atherosclerosis, and Mjalli suggests the liposomal delivery of benzimidazoles for the treatment of atherosclerosis.

In response, and for the same reasons discussed above, the Office Action has failed to establish a *prima facie* case of obviousness because the prior art references do not teach or suggest all the claim limitations. M.P.E.P. § 2143.

Aikawa II is merely relied upon to teach benzimidazole derivatives for the treatment of atherosclerosis. However, as acknowledged by the Office Action, Aikawa II does not teach the use of liposomes as carriers.

The additional reliance on Aikawa I, Kitaguchi, Schmidt, and Mjalli to cure the deficiencies of Aikawa II does not result in the presently claimed invention because none of the cited references teach or suggest the presently claimed liposome wherein the benzimidazole and lipid components are combined at the same time.

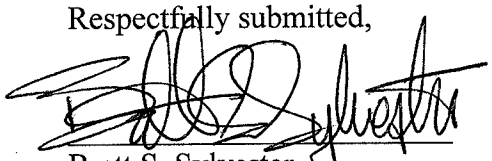
Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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